

## COMPARISON OF STENTING WITH MINIMALLY INVASIVE BYPASS SURGERY FOR STENOSIS OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY

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**ABSTRACT**

**Background** Minimally invasive bypass surgery and coronary-artery stenting are both accepted treatments for isolated stenosis of the proximal left anterior descending coronary artery. We compared the clinical outcomes after these two procedures.

**Methods** A total of 220 symptomatic patients with high-grade lesions in the proximal left anterior descending coronary artery were randomly assigned to treatment — 110 to surgery and 110 to stenting. The combined clinical end point was freedom from major adverse cardiac events, such as death from cardiac causes, myocardial infarction, and the need for repeated revascularization of the target lesion within six months.

**Results** A major adverse cardiac event occurred in 31 percent of patients after stenting, as compared with 15 percent in the surgery group ( $P=0.02$ ). The difference was predominantly due to a higher rate of repeated revascularization of the target vessel for restenosis after stenting (29 percent vs. 8 percent,  $P=0.003$ ). The combined rates of death and myocardial infarction did not differ significantly between groups (3 percent in the stenting group and 6 percent in the surgery group,  $P=0.50$ ). Adverse events occurred more frequently after surgery. The percentage of patients free from angina after six months was 79 percent in the surgery group, as compared with 62 percent in the stenting group ( $P=0.03$ ).

**Conclusions** In patients with isolated high-grade lesions of the proximal left anterior descending artery, both minimally invasive bypass surgery and stenting are effective. Stenting yields excellent short-term results with fewer periprocedural adverse events, but surgery is superior with regard to the need for repeated intervention in the target vessel and freedom from angina at six months of follow-up. (N Engl J Med 2002; 347:561-6.)

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**H**IGH-GRADE stenosis of the proximal left anterior descending coronary artery in patients with single-vessel disease is associated with a significantly worse prognosis than lesions at any other location.<sup>1,2</sup> Both percutaneous transluminal coronary angioplasty and coronary-artery bypass grafting have been shown to improve symptoms in such patients.<sup>3,4</sup> In several studies, the incidence of medium-term adverse events and

the proportion of patients requiring repeated revascularization of the target lesion were consistently higher after balloon angioplasty than after conventional coronary-artery bypass grafting in patients with single-vessel<sup>5,6</sup> or multivessel<sup>7-9</sup> disease. With the introduction of intracoronary stents, however, the rate of restenosis has been substantially reduced.<sup>10-12</sup> At the same time, minimally invasive direct coronary-artery bypass surgery, in which the left internal thoracic artery is used for grafting of the left anterior descending artery through a limited left thoracotomy performed on the beating heart, has substantially decreased the trauma associated with surgical treatment.<sup>13-15</sup> In this single-site, randomized study, we compared the merits of the two techniques for the treatment of patients with isolated lesions of the proximal left anterior descending coronary artery.

**METHODS****Study Patients**

Patients with isolated high-grade lesions (stenosis of  $\geq 75$  percent of the luminal diameter) in the proximal left anterior descending artery were included in the study. The lesion had to be confined to the segment between the origin of the left circumflex coronary artery and the first major septal branch. Patients were excluded if they had acute coronary syndromes requiring immediate intervention, additional clinically significant coronary lesions or valvular heart disease requiring treatment, or stenosis of the first diagonal branch or stenosis extending over a major diagonal branch or if they had previously undergone interventional or surgical treatment for coronary artery disease. Patients with total occlusion and patients with an intramyocardial course of the left anterior descending artery were also excluded, since minimally invasive surgery requires full visualization of the target vessel. The cardiac surgeon and the cardiologist had to agree on the eligibility of each patient before randomization. The study was approved by the local ethics committee. Written informed consent was obtained from all patients. Balanced randomization was performed by means of the drawing of sealed, unlabeled, unordered envelopes from an urn.

**Angiographic Analysis**

Angiography was performed in multiple projections after intracoronary application of nitroglycerin. Quantitative computed analysis was performed by an operator who was unaware of the patient's identity, using a validated image-processing algorithm (CMS, version 3.0, Medis). The diameters of the normal segments proximal

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and distal to the treated area were averaged to determine the reference diameter. Minimal luminal diameter and percentage of stenosis were calculated. In the surgery group, the reduction in luminal diameter was confined to the anastomotic site; therefore, no distal reference diameter of the internal thoracic artery could be obtained. Restenosis was defined as stenosis of more than 50 percent of the luminal diameter.

### Stenting Procedure

Stenting was performed according to standard clinical practice. The femoral approach was used, with a 6-French or 8-French guiding catheter. All patients began to receive 350 mg of aspirin per day and either 500 mg of ticlopidine per day or 300 mg of clopidogrel per day on the day before the procedure. Administration of ticlopidine or clopidogrel continued for a minimum of four weeks, and aspirin was given indefinitely. A bolus of 10,000 U of heparin was given at the beginning of the intervention. Selection of the balloon size was based on visual assessment of the target vessel. A balloon-to-vessel ratio of between 1.1 and 1.2 was recommended. Primary stenting without predilation was used whenever feasible. The choice of stent was left to the operator.

### Minimally Invasive Bypass Surgery

The technique of minimally invasive direct coronary-artery bypass surgery has been described in detail elsewhere.<sup>15</sup> In brief, a limited left anterolateral thoracotomy was performed through the fourth intercostal space. The internal thoracic artery was harvested under direct vision. After the administration of heparin (100 U per kilogram of body weight), the internal thoracic artery was divided distally. Local immobilization of the anastomotic site was achieved with mechanical stabilizers. The anastomosis was performed with the use of one running 8-0 polypropylene suture on the beating heart. Protamine was applied to neutralize 80 percent of the dose of heparin. Wounds were closed in a standard fashion.

### Follow-up

All patients were monitored for at least 24 hours. Creatine kinase activity was measured and 12-lead electrocardiography was performed immediately after the procedure and 6, 12, and 18 hours later. Patients assigned to surgery underwent angiography before discharge. Myocardial infarction was diagnosed either if the ratio of serum creatine kinase MB isoenzyme (CK-MB) to total cardiac enzyme exceeded 0.1 or if the CK-MB value was three times the upper limit of normal. In addition, standard electrocardiographic criteria were applied.

Six-month follow-up included a complete clinical workup with a symptom-limited exercise stress test and coronary angiography. In case of recurrence of angina, a positive stress test, or both, a repeated intervention was performed.

### Statistical Analysis

The primary composite end point was defined as freedom from major adverse cardiovascular events, which included death from cardiac causes, myocardial infarction, and the need for repeated revascularization of the target lesion within six months. Secondary end points included each individual component of the composite end point, the clinical status as assessed according to the Canadian Cardiovascular Society (CCS) classification,<sup>16</sup> and the need for antiangiinal drugs at six months of follow-up. In addition, periprocedural adverse events were documented.

The sample size was chosen in order to achieve 95 percent statistical power with a type I error of 5 percent with the use of a two-sided Fisher's exact test. In order to allow for losses to follow-up, we recruited 10 additional patients for each group. On the basis of previous reports, it was assumed that 30 percent of the patients treated by stenting and 9 percent of those treated by surgery would reach the combined primary end point.

All analyses were conducted according to the intention-to-treat principle. All events occurring after randomization were included in the analysis. Patients who were lost to follow-up were excluded from further analysis. In addition, patients who did not undergo repeated angiography were excluded from the calculation of the overall rate of restenosis (Fig. 1). Data for the categorical variables are expressed as the number and the percentage of patients. For continuous variables, data are reported as estimated means  $\pm$ SD, and values were compared by unpaired Student's *t*-tests after testing for normal distribution. Fisher's exact test or a chi-square test was used for categorical variables with nominal scales, and the Wilcoxon or Mann-Whitney rank-sum test was used for those with ordinal scales. Rates of events were compared by the calculation of unadjusted relative risks with 95 percent confidence intervals. All statistical tests were two-tailed. A *P* value of less than 0.05 was considered to indicate statistical significance. There were no interim analyses.

## RESULTS

### Study Patients

Between June 1997 and June 2001, 220 consecutive patients were randomly assigned to treatment — 110 to stenting and 110 to minimally invasive surgery. There were no significant differences between the groups with respect to demographic characteristics or base-line variables (Table 1). The mean ( $\pm$ SD) interval between randomization and treatment was  $2 \pm 3$  days (range, 0 to 23) among patients assigned to stenting and  $14 \pm 46$  days (range, 0 to 106) among patients assigned to surgery ( $P < 0.001$ ). All patients received the assigned treatment, and there were no adverse events in patients awaiting surgery or stenting.

### Clinical Outcome

#### Stenting

Stenting was successful in all patients, and there were no complications. The mean percentage of stenosis was significantly reduced (Table 2). An average of  $1.2 \pm 0.4$  stents were implanted at a mean stent-dilation pressure of  $13.3 \pm 1.7$  atm. The mean length of a stent was  $15.1 \pm 4.3$  mm. GFX stents (Medtronic) were used in 64 patients, Pura-Vario (Devon Medical) in 10, Inflow (Inflow Dynamics) in 9, Micro II (Arterial Vascular Engineering) in 7, MAC (AMG) in 10, MAC Carbon (AMG) in 4, and Sito (Jomed) in 6.

After stenting, a retroperitoneal hematoma developed in two patients; the hematomas were managed conservatively. One patient had an acute myocardial infarction due to early stent thrombosis, which was treated with balloon angioplasty and abciximab. In another patient who stopped taking aspirin and ticlopidine, subacute stent thrombosis developed two weeks after stent implantation; the occlusion was recanalized by balloon angioplasty. In one patient, a ruptured plaque in the left circumflex coronary artery caused an acute myocardial infarction two months after hospital discharge. Two patients died from strokes three months after the intervention.

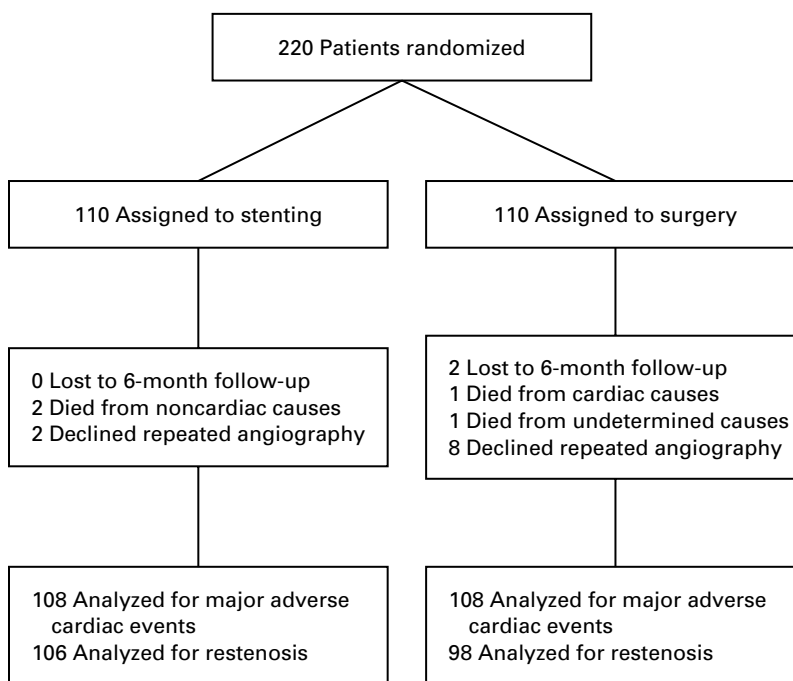


Figure 1. Numbers of Patients Included in the Analyses.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

VARIABLE	STENTING GROUP (N=110)	SURGERY GROUP (N=110)	P VALUE
Age — yr	62.5±10.2	61.6±10.0	0.61
Male sex — no. (%)	79 (72)	85 (77)	0.44
Body-mass index†	28.2±3.8	27.2±3.4	0.05
Cardiovascular risk factors — no. (%)			
Current smoking	27 (25)	27 (25)	1.00
Hypertension	79 (72)	78 (71)	0.97
Hypercholesterolemia	77 (70)	80 (73)	0.94
Diabetes mellitus	37 (34)	28 (25)	0.40
Family history of coronary artery disease	20 (18)	19 (17)	0.98
Previous myocardial infarction — no. (%)	49 (45)	50 (45)	0.97
Q-wave infarction	23 (21)	22 (20)	
Non-Q-wave infarction	26 (24)	28 (25)	
Left ventricular ejection fraction — %	62±15	63±11	0.92

\*Plus-minus values are means ±SD.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

TABLE 2. RESULTS OF QUANTITATIVE CORONARY ANGIOGRAPHY.\*

VARIABLE	BASE LINE	AFTER INTERVENTION	6 Mo
<b>Stenting</b>			
No. of patients	110	110	106
Percentage of stenosis	82.4±7.4	10.9±6.2†	45.4±24.9‡
Minimal luminal diameter — mm	0.53±0.23	3.13±1.49†	1.70±0.87
Reference diameter — mm	3.03±0.45	3.29±0.39†	3.03±0.43
Type of lesion — no. (%)			
A	18 (16)		
B	65 (59)		
C	27 (25)		
<b>Minimally invasive surgery</b>			
No. of patients	110	110	98
Percentage of stenosis	83.2±8.1	Not assessed	86.3±13.4‡
Minimal luminal diameter — mm	0.50±0.25	Not assessed	0.38±0.38†
Reference diameter — mm	2.94±0.44	Not assessed	2.74±0.39†
Type of lesion — no. (%)			
A	14 (13)		
B	70 (64)		
C	26 (24)		

\*Plus-minus values are means ±SD. Lesions were classified according to the system of the American College of Cardiology–American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures.<sup>17</sup>

†P<0.001 for the comparison with base line.

‡P=0.02 for the comparison with base line.

**Minimally Invasive Bypass Surgery**

Minimally invasive surgery was successfully performed in 95 percent of the patients in the surgery group. In five patients, conversion to a full sternotomy was necessary because of an intramyocardial segment of the left anterior descending coronary artery (in three patients), an injured internal thoracic artery (in one patient), and severe pleural adhesions (in one patient). These patients had an otherwise uneventful course.

Three patients underwent reoperation during the hospitalization for the first operation because of anastomotic stenosis or occlusion; two of these patients had a perioperative myocardial infarction during the first operation. In two patients, the anastomosis was erroneously performed on the first diagonal branch; in one of these patients, stenting of the native vessel had to be performed; the second patient had adequate perfusion of the territory of the left anterior descending artery. Two other patients had perioperative myocardial infarction despite grafts that were shown to be patent on angiography. One patient had an ischemic stroke five days after the procedure. Chest-wall hernia requiring surgical repair occurred in two patients during the six-months of follow-up.

One patient died during a maximal bicycle exercise test 10 days after surgery. Autopsy revealed rupture of the graft, which was probably caused by mechanical resuscitation. Another patient died at a rehabilitation center 15 days after surgery; since this death was not witnessed and no autopsy was performed, the cause of death could not be ascertained. During follow-up, one patient had an acute myocardial infarction due to a new lesion of the left circumflex artery, which was treated by stenting. The mean duration of hospitalization after surgery was  $9 \pm 4$  days (range, 4 to 36), as compared with  $2 \pm 3$  days after stenting (range, 1 to 28) ( $P < 0.001$ ).

**Follow-up Results**

Follow-up was complete for all patients except for two patients in the surgery group. Two asymptomatic patients refused repeated cardiac catheterization after stenting, as did eight patients after surgery (Fig. 1).

After surgery, the mean CCS angina class improved from  $2.6 \pm 0.9$  to  $0.3 \pm 0.7$  ( $P < 0.001$ ), and 79 percent of patients were free of angina. After stenting, the angina class improved from  $2.6 \pm 0.9$  to  $0.7 \pm 1.0$  ( $P < 0.001$  for the comparison with base line;  $P = 0.02$  for the comparison with the surgery group), and 62 percent were free of angina ( $P = 0.03$  for the comparison with the surgery group). Six percent of patients in the surgery group required antianginal drug therapy, as compared with 19 percent in the stenting group ( $P = 0.006$ ). Physical-work capacity, however, was similar in

the two groups (a workload of  $120 \pm 37$  W in the stenting group and  $127 \pm 34$  W in the surgery group,  $P = 0.15$ ).

At six months of follow-up, in-stent restenosis was detected in 35 patients, and 29 of these underwent repeated revascularization (by balloon angioplasty in 25 patients and surgery in 4 patients) for recurrent angina, a positive stress test, or both. Subgroup analysis showed a restenosis rate of 18 percent for type A lesions, 26 percent for type B lesions, and 56 percent for type C lesions ( $P = 0.008$ ). The classification of stenoses is based on a variety of morphologic criteria that assess the degree of complexity of the lesion.<sup>17</sup> In the surgery group, 18 patients had a stenosis of more than 50 percent of the luminal diameter at the anastomotic region or in the bypass graft; 5 of those patients required interventional treatment, and the other 13 patients, who were asymptomatic, were treated conservatively, since the restenoses at the anastomotic site were in the range of 50 to 60 percent of the luminal diameter.

There were significantly more repeated interventions after stenting than after surgery (Table 3). However, death from cardiac causes and myocardial infarction, alone or together, were uncommon, and the rates did not differ significantly between groups.

**DISCUSSION**

Stenting has become the preferred treatment for isolated lesions of the left anterior descending coronary artery. The combination of balloon angioplasty, stenting, and antiplatelet treatment has reduced the rate of acute dissections and restenoses even among lesions with complex morphology. Interventional approaches have therefore found widespread application, whereas primary surgical treatment is recommended in only a few cases, despite the lack of randomized studies comparing the two approaches.

Location of the lesion in the proximal left anterior descending artery has been defined as an independent risk factor for restenosis after balloon dilation,<sup>18</sup> as well as after stenting. Despite implementation of state-of-the-art techniques in our study, the restenosis rate remained essentially unchanged from previous studies, in which rates ranged from 33 percent to 44 percent.<sup>10,19,20</sup> In one study, a restenosis rate of only 19 percent was reported, but the investigators had excluded patients with well-known risk factors for restenosis, such as long lesions ( $> 15$  mm in length), small vessels ( $< 3$  mm in diameter), and a high mean percentage of stenosis.<sup>12</sup> In our study, stent implantation might have been suboptimal in some patients, since the final percentage of stenosis was more than 10 percent; this fact might be explained by the visual rather than quantitative assessment during the procedure. Another factor influencing the restenosis rate might be the use of

TABLE 3. MAJOR ADVERSE CARDIAC EVENTS DURING SIX MONTHS OF FOLLOW-UP.

EVENT	STENTING	SURGERY	P VALUE	RELATIVE RISK (95% CI)*
	GROUP (N=108)	GROUP (N=108)		
	no. (%)			
Death from cardiac causes	0	2 (2)	0.99	
Acute myocardial infarction	3 (3)	5 (5)	0.68	1.77 (0.41–7.58)
<30 days	2 (2)	4 (4)		
30 days–6 mo	1 (1)	1 (1)		
Acute myocardial infarction or death from cardiac causes	3 (3)	7 (6)	0.50	2.33 (0.34–43.73)
Revascularization of the target vessel	31 (29)	9 (8)	0.003	0.29 (0.09–0.65)
<30 days	2 (2)	4 (4)		
30 days–6 mo	29 (27)	5 (5)		
Any major adverse cardiac event	34 (31)	16 (15)	0.02	0.47 (0.21–0.89)

\*CI denotes confidence interval.

stents with a strut thickness of more than 100  $\mu\text{m}$ , which is also an independent risk factor for restenosis.<sup>21</sup>

Our results reflect the advantages and disadvantages of stenting of the proximal left anterior descending artery. Stenting is a safe intervention even in lesions with complex morphologic features. The rate of periprocedural adverse events is low, with stent thrombosis in 2 of 110 patients. However, only 2 percent of our patients received additional glycoprotein IIb/IIIa inhibitors, which is a potential limitation of the study. The incidence of early occlusions at the target site might have been reduced by the more frequent use of these platelet inhibitors, which have been shown to reduce the rate of periprocedural events, particularly among high-risk patients.<sup>22,23</sup> Our study confirms the predictive value of lesion morphology for the development of subsequent restenosis.<sup>24</sup> A restenosis rate of 56 percent was found among type C lesions, as compared with a rate of 18 percent among type A lesions. In contrast, in the surgery group, the risk of subsequent restenosis was independent of the type of lesion.

The major factors contributing to restenosis — elastic recoil and vessel-wall remodeling — are addressed by stenting. However, given that drug-eluting stents and intravascular radiation have not yet been approved for general use, there is currently no effective therapy for the prevention of neointimal proliferation.<sup>25,26</sup>

Previous studies have demonstrated two major clinical outcomes favoring conventional coronary bypass surgery (with a sternotomy and cardiopulmonary bypass) over balloon dilation without stenting for the treatment of isolated lesions in the proximal left anterior descending artery: more complete relief of angina and a reduced need for repeated revascularization.<sup>5,6</sup> Despite these benefits, many patients prefer the less

invasive catheter-based approach to conventional coronary bypass surgery.

The minimally invasive surgical approach minimizes surgical trauma by limiting the access to the heart and avoiding cardiopulmonary bypass. Medium-term patency rates similar to those achieved with conventional bypass grafting have been reported.<sup>27</sup> A recent study demonstrated a survival rate of 98 percent and a rate of repeated revascularization of less than 2 percent.<sup>15</sup> The limited thoracotomy preserves sternal integrity and allows for a more rapid return to daily activities. More important, the avoidance of cardiopulmonary bypass reduces the immune response, preserves blood components, and improves postoperative neurocognitive function as compared with conventional cardiac surgery.<sup>28,29</sup> However, the limited access makes the procedure more challenging technically and may impair the quality of the anastomosis,<sup>14,30</sup> which is reflected in our study by a 3 percent rate of early reoperation for acute graft failure, two cases in which the anastomotic site was erroneously selected, and a 5 percent rate of conversion to full sternotomy.

After six months, all bypass grafts were patent, but irregularities at the anastomotic site were demonstrated by angiography in 18 percent of cases. This rate of irregularities can be partially attributed to the fact that, in contrast to other studies, our study used quantitative coronary angiography that is more sensitive than qualitative assessment in detecting restenosis.<sup>14,31</sup> However, repeated revascularization was necessary in only 5 percent of the patients, since most of the stenoses were in the range of 50 to 60 percent of luminal diameter. The limited degree of restenosis is also reflected by the more complete relief of anginal symptoms in the surgery group than in the stenting group. In studies comparing balloon angioplasty with bypass

surgery, such differences were attenuated during later follow-up because of additional revascularization procedures.<sup>6,9</sup>

Minimally invasive surgery is still a relatively new technique. Therefore, future developments and improved patient selection may further reduce periprocedural morbidity and the rate of early reinterventions. Because of the single-center design of this study, only experienced surgeons and interventional cardiologists participated in the trial. Finally, longer follow-up will be needed to address the long-term efficacy and costs of either stenting or surgery, since the efficacy of any therapy will be increasingly weighed against its costs.

Both stenting and minimally invasive bypass surgery are safe and effective treatment options for high-grade lesions in the proximal left anterior descending artery. Although stenting is the only truly minimally invasive therapy associated with fewer periprocedural events than surgery and can be considered the first-line option for lesions without complex morphologic features, surgery provides excellent outcome irrespective of the morphology of the lesion. Our study demonstrates that decisions about how to treat an isolated lesion in the proximal left anterior descending artery require an interdisciplinary approach. Patients should be informed about the alternative treatment options and about the rates of success and of periprocedural events among patients with lesions morphologically similar to theirs.

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